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Session 3

Use of Clinical Outcome Assessment Tools in Multinational Trials

Ashley Slagle, MS, PhD
Study Endpoints
Office of New Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
April 1, 2015

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Session 3 Participants

Speakers

- Maria Isaac, MASc, MD, PhD, MFPM, EMA
- Andrew Mulberg, MD, FAAP, FDA
- Donald Patrick, PhD, MSPH, University of Washington
- Debra Silberg, MD, PhD, Shire
- Laura Lee Johnson, PhD, FDA

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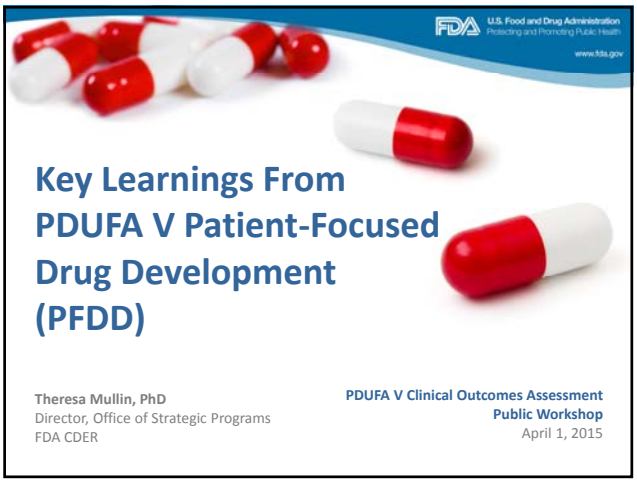

Key Learnings From PDUFA V Patient-Focused Drug Development (PFDD)

Theresa Mullin, PhD
Director, Office of Strategic Programs
FDA CDER

PDUFA V Clinical Outcomes Assessment Public Workshop
April 1, 2015

PFDD Work to Date

- FDA is convening 20+ meetings to obtain patient perspectives in specific disease areas
- Questions FDA asks in these meetings include:
  - Which symptoms have the most significant impact on your daily life?... On your ability to do specific activities?
  - How well does your current treatment regimen treat the most significant symptoms of your disease?
  - What specific things would you look for in an ideal treatment for your condition?
  - What factors do you take into account when making decisions about using treatments? …. Deciding whether to participate in a clinical trial?

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PFDD meetings FY 2013-2015

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction *To be conducted* • Breast cancer (April 2) • Chagas disease (April 28) • Functional gastrointestinal disorders (May 11) • Alpha-1 antitrypsin deficiency • Parkinson's disease and Huntington's disease

In-Person	Registered	Attended
Patient / Representatives	40 – 185	30 - 80
Other (e.g., NIH, industry)	40 – 115	30 - 140
Webcast	250 - 650	~50% of registered
Docket Submissions	5 - 400	

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PFDD Learnings to Date

- Patients with chronic serious disease are experts on what it's like to live with their condition
- They want their experience described using words that they consider to best describe how it feels
- Among the diseases in PFDD meetings to date, the most prominent impacts (symptoms, loss of function) are primarily physiological and often observed and confirmed by other family members
- For progressive degenerative diseases many patients/parents feel an ideal treatment would at minimum stop progression of their/their child's loss of function

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PFDD Learnings to Date (cont)

- Patients' "chief complaints" may not be factored explicitly into drug development plans, including measures of drug benefit planned in trials
- Patients want to be as active as possible in the work to develop and evaluate new treatments
- They and their caregivers are able and willing to engage via the Internet, social media, and all other means at their disposal
- They are not expecting for FDA to address all the gaps in current treatment or current approaches to drug development but do want FDA to help identify most effective pathways for them to play major contributing role

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FDA Potential Next Steps

- Advance science of patient input engaging wider community to discuss:
  - Methodologically sound approaches to bridge from initial patient-focused meetings to more systematic collection of patients' experience living with a particular disease
  - How to best proceed in obtaining patients' reports, assessments, and preferences, to inform patient-centered development and benefit risk assessment.
    - Approaches to recording patients' experiences of impact (burden) of disease over time
    - Understanding preferences for treatment impacts and tolerance of uncertainty about meaningful, significant potential benefits versus harms
- Provide guidance to patient advocates and drug developers

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Where Do We Go From Here?

Questions for our Session 4 Panelists--

From their perspective:

- *What are key elements of strategy going forward?*
- *What actionable next steps do you think need to be taken in the next 2-5 years?*

CDER - Office of Strategic Programs (OSP) 7

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Practical Advice on the Development and Use of Clinical Outcome Assessment Tools in Multinational Trials

Laura Lee Johnson, Ph.D.
Office of Biostatistics
Center for Drug Evaluation and Research
Food and Drug Administration

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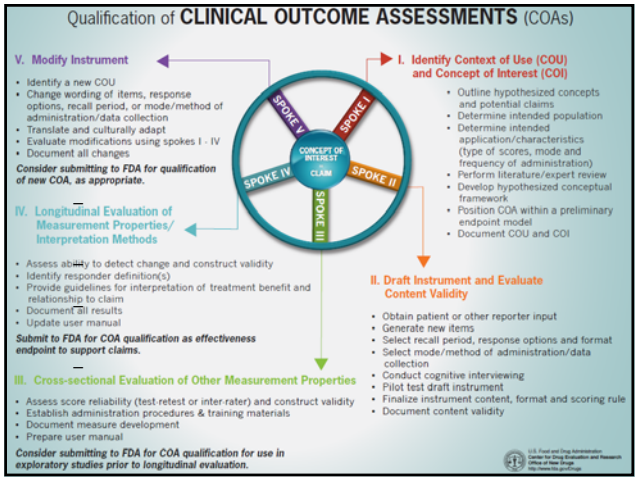
Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.



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Risk and Benefit to Early Translation

- Backing in to cognitive, pediatric, and multi-regional issues can be costly
- Broad development work is also costly
- Practical advice
  - Drug development timeline
  - Pooling data
  - Data collection issues
- "Review Issue"

Not Only COAs

CS-14

Stroke or SEE by Region
mITT On-Treatment

Endpoint Region	Pts	HR	← Edoxaban better / Warfarin better →	$CHADS_2$ score	Median C_{av}	Median TTR
Stroke or SEE						
Overall	14,024	0.79		2.8	79	68
North America	3115	0.55		2.8	76	73
Latin America	1769	0.47		2.9	82	66
Western Europe	2145	1.47		2.8	83	72
Eastern Europe	4752	1.00		2.9	79	66
Asia/Pacific	1570	0.54		2.8	76	63
Japan	673	0.95		2.8	73	72

0.25 0.5 1 2 4
Hazard ratio (95% CI)

Daiichi-Sankyo presentations for the October 30, 2014 Meeting of the Cardiovascular and Renal Drugs Advisory Committee, Slide 87 (Subgroup Analyses) by Glenn Gormley, MD, PhD http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421613.pdf. Downloaded 30 March 2015

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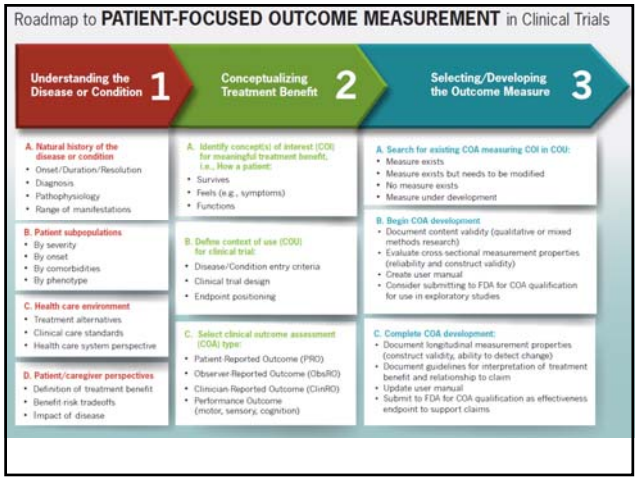
Early!

- When to think about
  - Translatability
  - Translation
  - Adaptation
- Literacy
- Pediatrics
- Multi regional studies



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Many Good Practice Guidelines Available

- They do not differ that much
- Using and citing them will go a long way
- There are costs to NOT attending to these issues early

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Further Information

- ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data (www.ich.org)
  - The Q&A section is especially helpful
- Multi-regional Clinical Trials – Considerations in Design and Analysis, Aloka G. Chakravarty, Ph.D. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM420084.pdf

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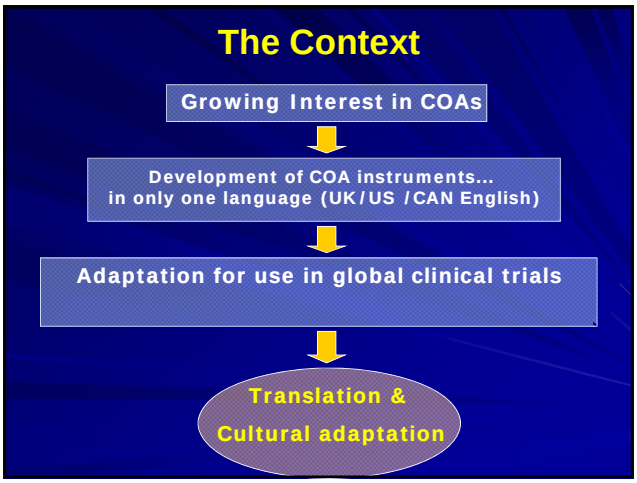
Thank You

Cultural Adaptation of Clinical Outcome Assessments in Multinational Trials

Donald L. Patrick, PhD, MSPH
University of Washington

Presentation at PDUFA V Clinical Outcomes Assessment Public Workshop
White Oak Campus, Food and Drug Administration, 1 April 2015

The Context



Differences in COAs require new considerations in cultural adaptation

EXAMPLES:

What is the appropriate adaptation process when doctors ask patients questions in their interview and their answers generate trial data?

- How should patients, clinicians and observers be involved in the translation process for the specific COAs?
- How does the process accommodate growing migrant populations and sub populations?
- What new considerations are needed for use with the wide variety of electronic platforms and devices?

Why is a specialized methodology necessary?

Globalization of Clinical Research: Over 60% of pivotal studies submitted to CDER in 1967 contained data from one or more foreign study sites (6 out of 10 of the studies)*

Need for cross-cultural equivalence to allow for pooling and comparison of data across countries

Cultural adapation first step towards achieving and testing cross-cultural equivalence.

*Ayalew K. FDA Perspective on International Clinical Trials. December 12, 2013 http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM378499.pdf

Why is it important to do more than basic translation?

Why do we need cultural adaptation?

Translation - Cultural Adaptation

- **Translation**
  - Act of bilingual communication
  - *(a rendering from one language into another;* also**:** *the product of such a rendering* Merriam Webster)
  - Made possible because of parallelisms in thoughts and situations = transcoding operation
  - (representation of reality is coded differently in different languages)
- **Cultural Adapation**
  - Process used to make COAs useful in multiple languages\cultures
  - Implies several steps, using translation techniques, but also test on target populations (patients or healthy subjects)
  - More than a simple translation

Orange Campaign in UK

"The future's bright – the future's Orange"

Orange was a mobile network operator and internet service provider in the United Kingdom, launched in 1993. 2009: Orange UK has since merged with Deutsche Telekom's T Mobile UK to form a joint venture, EE.

Not for the Catholics of Northern Ireland!!

They do not see the future as Protestant!

Example in conceptual analysis

Questionnaire: Health Assessment Questionnaire (HAQ)

- Original: US English
- Eating category: **Are you able to cut your meat?**
- What is the concept behind this item?
- Concept: to assess patient's ability to do micro movements of the upper extremity (functional ability)

Item in Cultural Adaptation

Questionnaire: Health Assessment Questionnaire (HAQ)

- Original: US English
- Eating category: **Are you able to cut your meat?**
- Target language: **Hindi/India**
- Concept? To assess patient's ability to do micro movements of the upper extremity (functional ability).
- Linguistic/cultural problems?
  - Use of cutlery, vegetarianism
- *Solution:* **Are you able to break chapatis with your fingers?**

Example of Forward/Backward Step

Questionnaire: PROMIS Physical item bank

- Original: US English
- **Are you able to push open a door after turning the knob?**
- Target language: **Dutch**
- Concept: to explore patient's ability to use his/her hand (functional ability)
- Problem: doors with door knobs are quite uncommon in the Netherlands. Most doors have latches.
- Solution: **Are you able to push open a door after pushing down the latch?**

Oude Voshaar et al. Arthritis Research & Therapy 2012,14:R47 - http://arthritis research.com/content/14/2/R47

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An Approach: Translatability Assessment

- Evaluation of the extent to which a PRO measure can be meaningfully translated into another language.
- A "meaningful translation" in the context of international clinical trials is one that is conceptually equivalent to the source text and culturally and linguistically appropriate in the target country to facilitate the comparison and pooling of data.
- The goal of a TA is to identify translation difficulties and suggest items to be modified or identified for deletion ***before*** embarking on the translation process itself.

ISPOR Good Practices

Wild D, et al. ISPOR principles of good practice: the cross cultural adaptation process for patient reported. Value Health 2005;8:94 10.

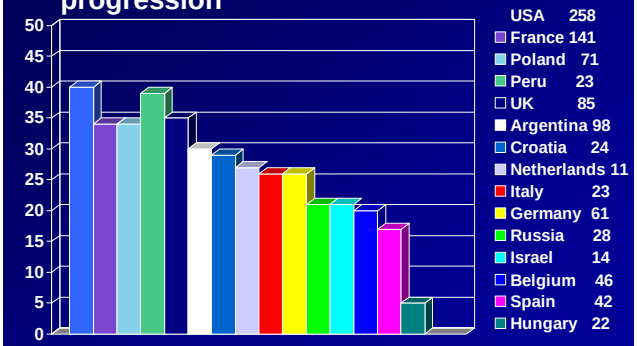
- Preparation
- Forward Translation
- Reconciliation
- Back Translation
- Back Translation Review
- Harmonization
- Cognitive Debriefing
- Review of all results and finalization
- Proofreading
- Final Report

How much can poor cross-cultural measurement affect statistical power?

- Study performed to explore the potential effect of the difference in the estimation of a PRO measure in a cultural group on the statistical power of the test comparing this measure between two treatment groups in the overall sample of a clinical trial.
- The impact of poor PRO measurement in a cultural subgroup can induce a notable drop in the study power and consequently reduce the chance of showing an actual treatment effect.
- This result illustrates the importance of the efforts to optimize cultural equivalence of PRO measures and standardization of assessments when pooling data in international clinical trials.

Regnault A, Hamel JF, Patrick DL. Pooling of cross-cultura PRO data in multinational clinical trials: How much can poor measurement affect statist cal power. QOL Research accepted 2014

Example: Pain and/or Analgesic progression



Summary

Cultural adaptation is a *complex* and *challenging* process

It is not a "word for word" translation

But a "world for world" translation

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Global Stakeholder Engagement for Pediatric and Adult Drug Development

Andrew E. Mulberg, MD, FAAP
Division Deputy Director, Gastroenterology and Inborn Errors Products
FDA

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International IBD (*i*-IBD) Working Group

- **Convened in 2012 (monthly teleconference Jan - Dec 2012 and current)**
  - **Consisted of regulatory scientists from: U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) , Health Canada, Pharmaceuticals and Medical Devices Agency of Japan (PMDA)**
  - **Goal: To facilitate global harmonization on regulatory issues affecting drug development in pediatric ulcerative colitis (UC). Topics discussed include: Extrapolation, Trial design, Disease outcome assessments , Efficacy endpoints, Pharmacokinetic considerations**

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International IBD (*i*-IBD) Working Group

- Recent Acceptance of Manuscripts for Publication: *Journal of Pediatric Gastroenterology and Nutrition* 2014
- Steps towards Harmonization for Clinical Development of Medicines in Pediatric
- Ulcerative Colitis --- a Global Scientific Discussion
  - Part 1: Efficacy Endpoints and Disease Outcome Assessments
    - Steps towards Harmonization for Clinical Development of Medicines in Pediatric
      - Ulcerative Colitis --- Global Scientific Discussion
  - Part 2: Data Extrapolation, Trial Design, and Pharmacokinetics

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GREAT 2012-2015

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Session 3: Use of clinical Outcome Assessment Tools in multinational trials: Qualification of Novel Methodologies

Maria Isaac, MASc, MD, PhD, MFPM, Psychiatrist

Senior Scientific Officer

An agency of the European Union

EUROPEAN MEDICINES AGENCY

Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood nor quoted as being made on behalf of or reflecting the position of EMA or one of its committees or working parties or any of the national agencies.

Other positions:

- Vice Chair of the Psychopharmacology Special Committee of the Council of the Royal College of Psychiatrists, UK.
- Previous : Consultant Psychiatrist & Co-Director of Psychopharmacology Evaluation Unit at the South London & Maudsley NHS trust in London and Honorary Senior Lecturer in the Department of Forensic and Neurodevelopmental Sciences at the Institute of Psychiatry, Kings College London, UK.

EMA committees

EUROPEAN MEDICINES AGENCY

SAWP

CHMP (Committee for Human Medicinal Products)

COMP (Committee for Orphan Medicinal Products)

HMPC (Committee for Herbal Medicinal Products)

PDCO (Paediatric Committee)

CAT (Committee for Advanced Therapy Medicinal Products)

PRAC (Pharmacovigilance risk assessment committee)

EU Guidance for Qualification of Novel Methodologies

EUROPEAN MEDICINES AGENCY

- New regulatory procedure (2008, revised in 2012, 2014)
- Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm
- One procedure with two outcomes:
- Qualification Advice, OR
- Qualification Opinion

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2009
Final Agreed by CHMP	22 January 2009
Keywords	EMA, CHMP, Novel methodology, Qualification, Scientific Advice, Biomarker

Long-term benefits from EMA prespective: Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisation applications

Scientific Advice Working Party

standing WP of the CHMP (Reg. 726/2004)

multidisciplinary expert group (28) selected by expertise (not MS)

16 National Competent Authorities, 12 academia; members of EMA committees 3 COMP, 1 CAT, 2 PDCO

CHMP peer-review, ad hoc discussions, adoption final advice letter

CMC: starting materials, specs, comparability, bridging…

non-clinical: overall toxicology plan registration, innovative models…

clinical pharmacology: PK/PD, modeling & simulation, BE…

clinical therapeutic areas: endpoints, population, comparator…

methodology, statistics: interim A, adaptive/seamless design…

network of external experts

Qualification of novel methodologies

CHMP qualification advice on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted, confidential

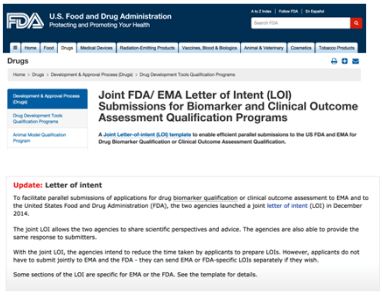
CHMP qualification opinion on the acceptability of a specific use of the proposed method (e.g. use of a BM) in a R&D context (non-clinical or clinical), based on the assessment of data, not product-specific. Qualification team, peer-review, public consultation, publication

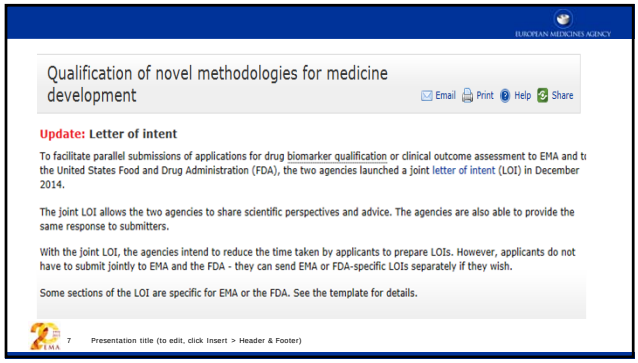
The procedural route is not fixed but will follow the assessment of the data

Aims: SAWP/CHMP early involvement in the design of the strategy, with commitment to evaluate data from agreed studies and to provide opinion

Scope: Focus on acceptability of specific use of the proposed technology/BM developed for a specific intended use in the context of pharmaceutical R&D (Context of Use)

FDA-EMA parallel Qualification ADVICE





FDA-EMA parallel Qualification ADVICE

- Encouraged by both Agencies
- Voluntary, at request of sponsor
- Discussion between FDA-EMA and tripartite meeting with sponsor
- Alignment of procedural flow between agencies is important and challenging: preparatory interactions with both agencies should start early
- Each Agency will issue separate responses to sponsor's questions in line with their usual procedures

→ Increased dialogue between Agencies and sponsor from early stages of development
→ Exchange views, share expertise
→ Optimise and facilitate global development, meeting both agencies requirements

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Draft — Not for Implementation

Guidance for Industry[1]
Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease

6 March 2015
EMA/CHMP/SAWP/178465/2015
Product Development Scientific Support Department

Draft Qualification Opinion of Qualification of Exacerbations of Chronic Pulmonary Disease Tool (EXACT), and EXACT-Respiratory Symptoms Measure (E-RS) for Evaluating Treatment Outcomes in Clinical trials in COPD

Draft agreed by Scientific Advice Working Party	5 February 2015
Adopted by CHMP for release for consultation	26 February 2015
Start of public consultation	23 March 2015
End of consultation (deadline for comments)	30 April 2015

Comments should be provided using this template. The completed comments form should be sent to Qualification@ema.europa.eu

Keywords	chronic obstructive pulmonary disease, clinical trial, COPD, endpoint, E-RS, exacerbation, EXACT PRO, patient-reported outcome, PRO, respiratory symptoms

CHMP Opinion

The CHMP concludes that the EXACT PRO currently can be used as an exploratory endpoint in drug development trials for the prevention of exacerbations in COPD. Not only the EXACT total score, but also the derived metrics for severity, duration and frequency of exacerbation events appear to be sufficiently sensitive to changes in an individual patient's disease condition.....

The E-RS is a derivative instrument from the EXACT designed to address the need for a standardized PRO measure for evaluating the effect of treatment on the severity of respiratory symptoms in stable COPD. ....

The CHMP concludes that the E-RS can be used as an exploratory endpoint in drug development trials evaluating the effect of treatment on respiratory symptoms of COPD.

Links

EMA guidance for companies requesting SA or PA

http://www.emea.europa.eu/pdfs/human/sciadvice/426001en.pdf

Qualification of novel methodologies for drug developments

http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf

Scientific guidelines

Http://www.emea.europa.eu/htms/human/humanguidelines/background.htm

Thank you for your attention

Further information

[maria.isaac@ema.europa.eu]

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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